EURL Cluster for VMP residues

CIR (EU) 2021/808

Overview of the "EURL Guidance document on the extension of quantitative confirmation methods"

Federal Office of Consumer Protection and Food Safety

EURL cluster website

European Commission

…on behalf of the 3 EURLs

https://eurl-residues.eu/

EURLs for Residues of Veterinary Medicinal Products

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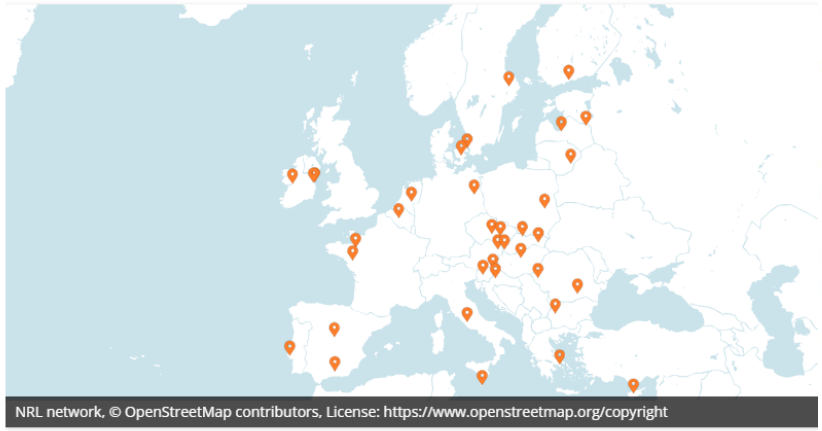

November 14, 2020

2024 EURL Berlin Proficiency Tests

The EURL Berlin is planning to organise two proficiency tests in 2024. Scheduled for the first and second quarter is a profi
ists in tissue (liver and lung). The participants will be provided with 3-4 test items produced from incurred samples.

For the third and fourth quarter we are planning a proficiency test on avermectins in bovine milk. For this PT we are also p
from incurred material.

Laboratories eligible for participation in any of the PTs will be contacted in due time regarding the registration process.

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Guidance Documents

The EURL Guidance Documents to Commission Implementing Regulation (EU) 2021/808 shall provide technical instructions for official control laboratories active in the field of veterinary drug residue analysis according to Regulation (EU) 2017/625. The documents' status will be that of associated documents to CIR (EU) 2021/808, representing the EURLs' interpretation of this document. Following the EURL Guidance Documents minutely will not be mandatory and different implementations are possible. However, a comparable level of quality must be achieved if deviation from the approaches outlined in the EURL Guidance Documents is intended.

Before the adoption of an EURL Guidance Document, an initial draft is prepared. From this, an EURL consolidated version is prepared which is then presented to the NRLs for discussion. The NRLs' comments are evaluated by the EURLs and the document amended before the publication of a first version. The EURL Guidance Documents are seen as 'living' documents and NRLs are welcome to submit their feedback in order to further improve the quality of the EURL Guidance Documents.

Currently, six technical EURL Guidance Documents have been published or are currently discussed:

- EURL Guidance Document on the quality control during routine analysis (ongoing method performance verification); finalised (version 1.2)
- EURL Guidance Document on confirmation method validation; finalised (version 1.1)
- EURL Guidance Document on the extension of methods; finalised (version 2.0)
- EURL Guidance Document on validation of screening methods; finalised (version 1.1)
- EURL Guidance Document on standard addition in the field of the analysis of residues of pharmacologically active substances; finalised (version 1.1, Spreadsheet MSA)
- EURL Guidance Document on the validation of HRMS methods

Furthermore, two EURL Guidance Documents on substances are available:

- EURL guidance on minimum method performance requirements (MMPRs) for specific pharmacologically active substances in specific animal matrices; finalised (version 2.0)
- EURL guidance on substances included in the substance categories listed in Annex I of SANTE 2017/11987 (draft Commission Implementing Regulation); currently under discussion within the EURLs

Extension of the scope of methods

Principles

(Chapter IV CIR (EU) 2021/808)

An extension of the scope can/should be accomplished in an **efficient and analytically sound** way. This can be achieved by carrying out a validation on **a reduced number of samples** compared to a full validation.

The type and number of modifications to be validated in a single reduced validation scheme shall always **be based on expert knowledge and previous experiences**, e.g. a change in detection technique would require a complete validation in any case.

Ideally, this **ongoing method performance control** is designed in a way that the missing data for a complete validation can be collected over time (e.g. with a few data points from QC samples in each analytical series).

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Extension of the scope of methods

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Principles

(Chapter IV CIR (EU) 2021/808)

4.1. Extensions of methods as regards to the range of concentrations

Due to changes of MRLs, MLs, and RPAs it may become necessary to adjust the concentration range for which a method is validated. For such a case, the application of **a reduced validation scheme is acceptable**.

4.2. Extensions of methods as regards to additional substances

Generally, the method extension to additional compounds is only possible for analytes, which **are similar structure** and characteristic-wise compared to those already included in the analytical method. For such a case, the application of a reduced validation scheme is acceptable. Likewise, **no divergence** from the method description is allowed.

Extension of the scope of methods

Principles

4.3. Extensions of methods as regards to matrices/species

The inclusion of new matrices or species in an already validated analytical method shall always be **a case-by-case decision based on the knowledge and experiences** gained so far with the method and preliminary experiments assessing potential matrix effects and interferences. Generally, this will only be possible for matrices that exhibit similar properties and for non-critical analytes (stability, detectability).

In cases **where MRLs** for a specific substance **differ for certain matrices**, it will most likely be difficult to adapt the method scope to the additional matrix/species and concentration, since in this case two modifications have to be considered. In such cases **a full validation is recommended**.

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EURL Guidance

European Commission

Version 2.0, 27 June 2023
EURL Guidance on Extension of quantitative confirmation methods

European Union Reference Laboratories supported by the European Commission

EURL Guidance document on the extension of quantitative confirmation methods

The contents of this document act as a guidance on how to implement the requirements of Commission Implementing Regulation 2021/808.

Contents

Version 2.0 – Table 2 updated for experimental design

1. Introduction

1.1. Scope

1.2 Extension of method

2. General considerations on the extension of methods

2.1. Analytes

2.2. Concentration range

2.3. Species and matrices

2.4. Changes to the method

EURL Guidance

4. Changes in the method

   small changes, e. g. a change of LC or GC column from one supplier to another, a new or another IS or a change of LC or GC system

= > Is it a major change ?

Practical implementation of reduced validation schemes

Experimental designs for

- the “conventional validation approach”
- the “alternative validation approach”

Extensions

… the type and number of modifications to be validated in a single reduced validation scheme should always be based on expert knowledge and previous experiences ….

- Extension is possible when no major divergence of the method is needed.

– **Documentation** of reasons !

…based on previous experiences ….!

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Major Change ?

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Concentration ranges

	Example A	*Example B*	*Example C*
Previous MRL	500	500	500
Minimum validated concentrations to be covered by the concentration range (0.1 (-0.5), 1.0, 1.5*MRL)	50 (-250), 500, 750	50 (-250), 500, 750	50 (-250), 500, 750
concentration range in the initial validation	50-750	50-750	10-750
Revised MRL	20	250	400
Minimum validated concentrations to be covered by the concentration range (0.1 (-0.5), 1.0, 1.5*MRL)	2 (-10), 20, 30	25 (125), 250, 375	40 (-200), 400, 600
Exemplary concentration range for the revised validation	0-50	(20-750) revision recommended	No revision required

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Overview of samples

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	Conventional, full	Conventional, extension	Alternative, full	Alternative, extension
Matrix calibration	3 x 5 =15	1 x 5 = 5	8 x 5 = 40	4 x 5 = 20
Specificity (only analytes, not IS)	3 x 7 = 21	1 x 6 = 6	8 x 1 = 8	4 x 1 = 4
Fortified samples	3 x 3 x 7 =63	1 x 3 x 6 = 18	8 x 5 = 40	4 x 5 = 20
Ruggedness	1 x 6 = 6	Not included in reduced scheme	Included by design	Included by design
Σ	**105**	**29**	**88**	**44**

Minimum sample numbers without :

Relative matrix effect
Standard calibration
Quality control samples
Stability

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Experimental plan (conventional)

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Sample	Purpose	Batch	Level Unauthorised ISO 11843	Level Unauthorised	Authorised
1	Calibration (matrix or standard solution)	A	0	0	0
2	Calibration (matrix or standard solution)	A	0+[1]	0+[1]	0+
3	Calibration (matrix or standard solution)	A	0++	0++	0++
4	Calibration (matrix or standard solution)	A	0+++	0+++	0+++
5	Calibration (matrix or standard solution)	A	0++++	0++++	0++++
6	Specificity	A	0	0	0
7	Specificity	B	0	0	0
8	Specificity	C	0	0	0
9	Specificity	D	0	0	0
10	Specificity	E	0	0	0
11	Specificity	F	0	0	0
12	CCα	A	Level 1	-	-
13	CCα	B	Level 1	-	-
14	CCα	C	Level 1	-	-
15	Trueness, repeatability at 0.1*MRL/ML	A	-	-	Level 1
16	Trueness, repeatability at 0.1*MRL/ML	B	-	-	Level 1
17	Trueness, repeatability at 0.1*MRL/ML	C	-	-	Level 1
18	Trueness, repeatability at 0.1*MRL/ML	D	-	-	Level 1
19	Trueness, repeatability at 0.1*MRL/ML	E	-	-	Level 1
20	Trueness, repeatability at 0.1*MRL/ML	F	-	-	Level 1
21	Trueness, repeatability, confirmation, CCα	A	Level 2	Level 1	Level 2
22	Trueness, repeatability, confirmation, CCα	B	Level 2	Level 1	Level 2
23	Trueness, repeatability, confirmation, CCα	C	Level 2	Level 1	Level 2
24	Trueness, repeatability, confirmation, CCα	D	Level 2	Level 1	Level 2
25	Trueness, repeatability, confirmation, CCα	E	Level 2	Level 1	Level 2
26	Trueness, repeatability, confirmation, CCα	F	Level 2	Level 1	Level 2
27	CCα	A	Level 3	-	-
28	CCα	B	Level 3	-	-
29	CCα	C	Level 3	-	-

[1] More '+' means higher fortification level

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Method extension using the alternative validation approach

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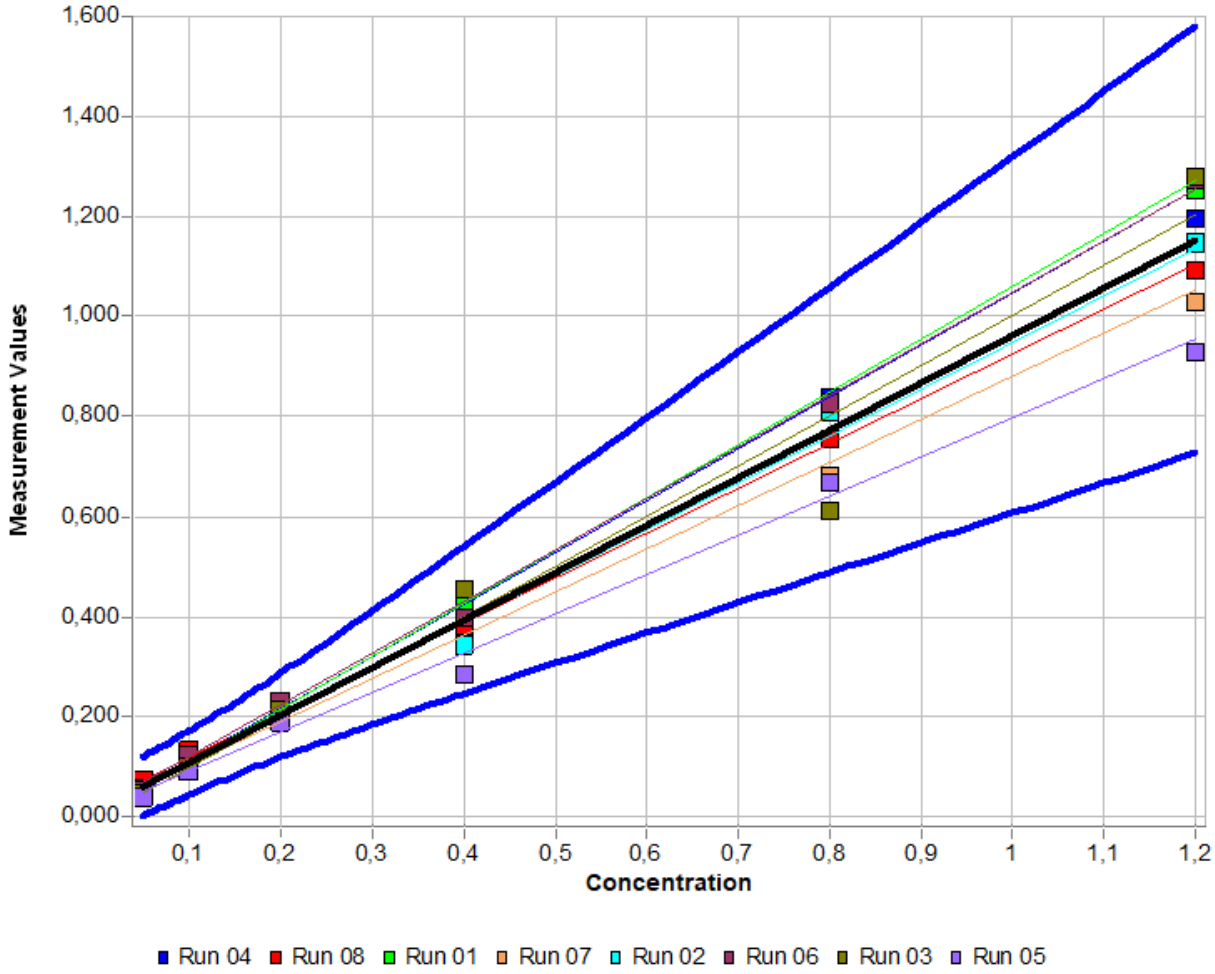
A well established method for nitroimidazoles in muscle and plasma is available

= > Plan : Extension of the method to milk

- Preliminary experiments suggest that method might be applicable to milk

Run	Species	Matrix	Operator	Amount of matrix	Storage of extract	Filtration	Final volume
Run 01	pig	muscle	unfamiliar	2 g	2-3 days of storage at +4 °C	no	200 µL
Run 02	pig	muscle	familiar	2 g	immediate analysis	yes	120 µL
Run 03	turkey	muscle	unfamiliar	1 g	2-3 days of storage at +4 °C	yes	120 µL
Run 04	turkey	muscle	familiar	1 g	immediate analysis	no	200 µL
Run 05	pig	plasma/serum	unfamiliar	1 g	immediate analysis	no	120 µL
Run 06	pig	plasma/serum	familiar	1 g	2-3 days of storage at +4 °C	yes	200 µL
Run 07	turkey	plasma/serum	unfamiliar	2 g	immediate analysis	yes	200 µL
Run 08	turkey	plasma/serum	familiar	2 g	2-3 days of storage at +4 °C	no	120 µL

Validation Evaluation (graphical)



8 runs

Mean calibration curve

Confidendence interval

CCα calculation

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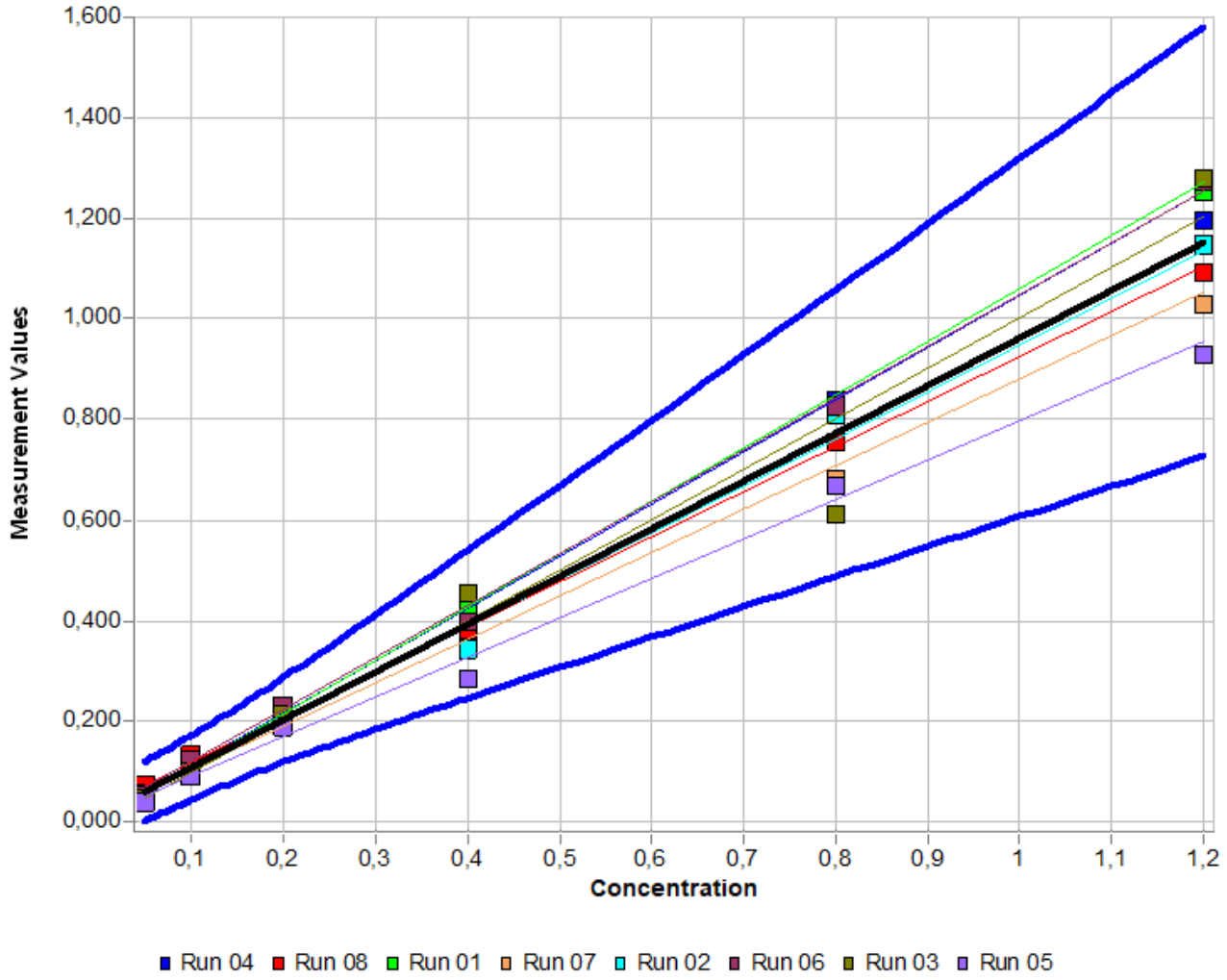
Method extension using the alternative validation approach

European Commission

- Factor 'species' has to be disregarded
- Choose 4 runs to repeat with the new matrix
- Factor levels for the runs to be repeated need to be equally distributed

Run	Species	Matrix	Operator	Amount of matrix	Storage of extract	Filtration	Final volume
Run 01_2	pig	~~muscle~~ milk	unfamiliar	2 g	2-3 days of storage at +4 °C	no	200 µL
Run 02_2	pig	~~muscle~~ milk	familiar	2 g	immediate analysis	yes	120 µL
Run 03_2	turkey	~~muscle~~ milk	unfamiliar	1 g	2-3 days of storage at +4 °C	yes	120 µL
Run 04_2	turkey	~~muscle~~ milk	familiar	1 g	immediate analysis	no	200 µL
Run 05	pig	plasma/serum	unfamiliar	1 g	immediate analysis	no	120 µL
Run 06	pig	plasma/serum	familiar	1 g	2-3 days of storage at +4 °C	yes	200 µL
Run 07	turkey	plasma/serum	unfamiliar	2 g	immediate analysis	yes	200 µL
Run 08	turkey	plasma/serum	familiar	2 g	2-3 days of storage at +4 °C	no	120 µL

Extension Evaluation (graphical)



Run 1-2-3-4
Milk

Run 5-6-7-8
muscle

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Method extension using the alternative validation approach

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- Factor level influence is comparable and not critical

Example: metronidazole		*Initial validation for muscle and plasma/serum*		*Method extension for milk and plasma/serum*		
Factor	*Level*	*Proportional deviation*	*Constant deviation*	*Proportional deviation*	Δ ✓	*Constant deviation*
matrix	plasma / serum(+); milk/muscle(-)	0.133	0.275	1.690	**+1.557**	1.984
species	pig (+); turkey (-)	1.126	0.980			
operator	unfamiliar (+); familiar(-)	-2.556	-1.178	-2.246	**+0.310**	-1.154
amount of matrix	2 g(+); 1 g(-)	0.982	0.129	0.675	**-0.295**	0.124
storage of extract	direct analysis(+); 2-3 days of storage(-)	-0.225	-0.012	0.285	**+0.510**	0.143
filtration	yes (+); no(-)	-2.246	-2.036	-0.132	**+2.114**	-0.109
volume	200 ul final volume(+); 120 ul final volume(-)	2.327	2.244	0.178	**-2.149**	0.300

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Method extension using the alternative validation approach

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- Evaluation by combining data from 4 repeated runs and data from old plasma/serum runs
- Requirements of CIR 2021/808 are fulfilled
- Parameters of initial validation and revised validation are in the same range

	Initial validation for muscle and plasma/serum			*Method extension for milk and plasma/serum*					
Analyte	*CC_α*	*Recovery [%] at CC_α*	*Relative reproducibility standard deviation s_R [%] at CC_α*	*CC_α* ✓	Δ	*Recovery [%] at CC_α* ✓	Δ	*Relative reproducibility standard deviation s_R [%] at CC_α* ✓	Δ
Dimetridazole	0.153	108.5	10.2	0.131	-0.022	109.2	+0.7	7.4	-2.8
HMMNI	0.163	106.8	13.5	0.200	+0.037	98.2	-8.6	18.1	+4.6
Metronidazole	0.072	107.0	10.7	0.068	-0.004	104.7	-2.3	9.0	-1.7
MNZOH	0.153	100.2	12.0	0.159	+0.006	103.2	-3.0	11.6	-0.4
Ronidazole	0.109	93.1	18.9	0.081	-0.028	102.2	+9.1	13.4	-5.5

Method extensions...

Considerations

The results of a successfully conducted reduced validation scheme can be accepted as a contribution to proving the fitness for purpose of the method.

The modified method may henceforth be applied.

To assure the validity of this assumption **the method performance shall be monitored continuously** and compared to the initially obtained validation parameters.

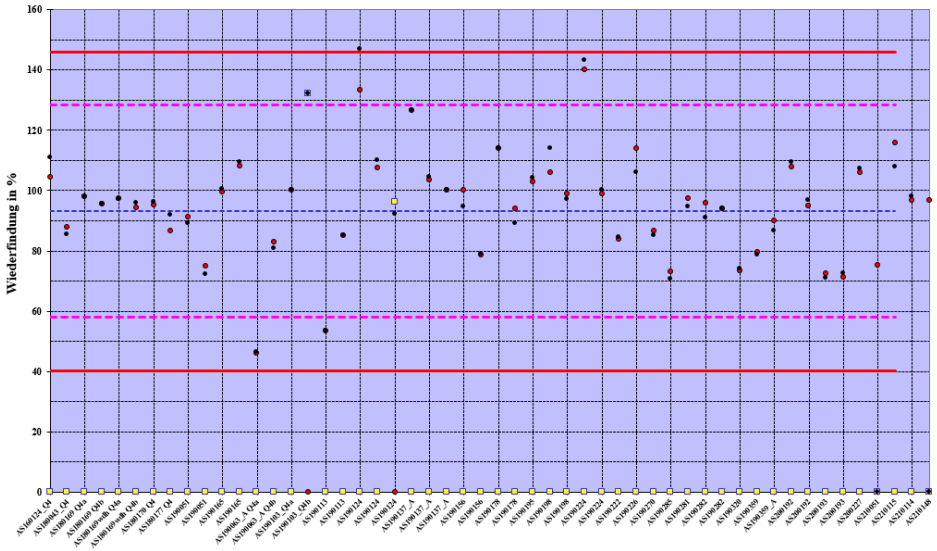
Recommendations...

Make use of ongoing method performance control !

Ideally, this ongoing method performance control **is designed /planned** in a way that the missing data for a complete validation can be collected over time (i. e. a few data points in each analytical series).

Internal QC

Gives an idea of the validity of the calculated measurement uncertainty



Recovery control chart – warning limit 2s

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Thanks for your attention !

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